Comments on the ICH S7B draft consensus guideline 'Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals'

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The members of the Expert Working Group should be acknowledged for the great effort that has gone into preparing the Step 2 guideline. The topic of "Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation)" is a difficult area to regulate given the limited database from which guidelines are to emerge. The challenge to the ICH members is also significant since the impact of the guidelines on the decisions towards developing novel new therapies for unmet medical needs will be significantly impacted by the outcome of the studies that are mandated prior to starting clinical trials.

A. General Comments:

1. **The concept that any signal at any concentration is a human risk, irrespective of human exposure at efficacy, poses an unrealistic hurdle that may lead to a decision to delay or discontinue the development of a promising new drug. The members are encouraged to find a way forward in revision of the Step 2 guideline to provide some boundary above which in most cases, but not necessarily all cases, a margin of safety can be applied to the interpretation of risk associated with non-clinical findings.**
2. References to metabolites in the document should clearly state that reference is being made to major metabolites. Attempts should be make to define 'major' metabolites.
3. In the guidelines, there is a great burden placed on the sponsor to investigate negative findings whether they are generated in preclinical or clinical investigations. The members should carefully review the text of the document to judge whether there is value added in requiring additional investigation or whether this objective may be achieved by other means. For example, it may not be possible to achieve adequate free drug levels to affect ventricular repolarization due to other adverse effects at the higher exposure levels.
4. The guidelines also indicate that the sponsor should consider the investigation of positive findings when discrepancies exist between preclinical and clinical studies, where positive findings are noted in the clinical studies. In this situation, a positive signal has been noted in humans and the safety of the drug can be determined based on the doses needed for efficacy. Any further investigation at this point of development should be at the discretion of the sponsor. The members should carefully review the text of the document to judge whether there is value added in this requirement for additional investigation.

B. Specific Comments:

1. Line 66; Is the fact that *in vitro* and *in vivo* assays are complementary approaches sufficient reason to mandate that more than one type of assay should be conducted? There should be a stronger justification for conducting multiple assays given the amount of work and time that is involved in adhering to the S7B mandated studies.
2. Line 74; this is reasonably a significant principle that clinical data will supercede preclinical data. However, at a later section of the guidelines, the suggestion is made that negative clinical findings in the presence of a preclinical signal (the guidelines do not consider margins of safety) should be investigated further in non-clinical studies. This strategy appears counter to the position articulated in line 74.
3. Line 105; Carefully designed and conducted *in vivo* studies **may** also….
4. Decision tree; line 119
   - The use of pharmacologic/chemical class as a positive signal appears excessive since this is based on association, but not on data for a particular drug. The strategy presented in S7B contains extensive non-clinical testing from which data will be available to judge the hazard/risk posed by a new molecule. The references to pharmacologic/chemical class can be made in the text (e.g. line 133) of the document, but not as a point of decision of whether a molecule is positive.
   - As noted above, the concept that any signal is a signal of risk, irrespective of the concentration at which this signal appears carries significant implications for the future of a drug that may not be deserved.
   - The decision tree indicates that based on the results of further *in vitro/in vivo* studies a positive signal may be considered “an artifact”. The types of follow up studies that would lead in this direction should be more clearly described. Also, types of studies that lead to the designation of “an artifact” should also be better explained. Otherwise, it is unclear how one transitions from a positive signal to “no signal of potential risk”.
   - The decision tree suggests that four levels of testing are mandated before the start of clinical trials. The sponsor should have the flexibility to decide that a positive signal in any one of the assays is sufficient to define a “signal of risk” and that clinical investigations can proceed with appropriate monitoring. If the members agree, then this option should be clearly stated in the guidelines. (refers to line 175)
5. Line 133; what is meant by many? What is the impact of an absence of preclinical findings on a drug that originates from a class associated with a signal? This should be articulated in the document and clarified in the decision tree, should Pharmacologic/Chemical Class remain in the decision tree.
6. Paragraph 142; enhanced study
   - The definition and value of the enhanced study is not clearly presented. If this is a second study in addition to the standard study/core battery cardiovascular study than such a study would not avoid the unneccessary use of animals. The core battery cardiovascular study as defined by S7A is comprehensive and detailed. The integrity of the data from such a study is robust. Other than for pharmacokinetic reasons where steady state concentrations of drug are achieved

or where cardiovascular toxicity emerges after multiple dosing, the value of conducting multiple dose studies at this stage of development should be carefully considered before being mandated by guidelines. The document should exclude reference to “enhanced” studies or clearly define their difference from “standard” studies and why ICH S7A Core Battery Studies (“standard”) are not sufficient.

- It is unclear what is meant by “other cardiovascular parameters”. The core battery study as defined by S7A is very comprehensive.

7. Line 152; “is the result of an artifact”; this statement is unclear and should be clarified.
8. Line 179; what if the standard in vivo study does not reveal a QT signal, but that this lack of effect can be explained by the large margin between concentration required to inhibit hERG and the maximum plasma level achieved at a dose which the animal is able to tolerate. The enhanced study would not resolve such a discrepancy. **The guidelines need to provide a greater level of direction than to indicate that any signal irrespective of exposure is a signal of risk.**
9. Line 185; this requirement places additional burden on the preclinical group to demonstrate a negative finding in the relevant species, man. The recommendation should not be to conduct additional studies, but rather to consider the existing data that may explain the differences between humans and animals.
10. Line 205; however, even large margins of safety… This is an extremely strong statement. Refer to the General Comment #1 above.
11. Line 242; **myocardium;** isolated, intact heart…
12. Line 256; In view of the position that any signal is a signal of risk, testing to the limits of solubility or limits based on physicochemical properties poses an unreasonable context in which to evaluate the data. The members are encouraged to discuss the concept of testing to some multiple of human exposure (e.g. 100 fold free drug) as a basis for selecting concentrations for the *in vitro* studies.
13. Line 266; Consideration should be given to the value of testing where the concentration tested *in vitro* is limited by solubility and is less than or equal to the concentration anticipated for efficacy. The guidelines should suggest that in such a situation, in vitro testing is not necessary and that *in vivo* testing will be used to determine the safety of a drug.
14. Line 268 refers to safety margins determined for *in vitro* testing. Line 279 appropriately distinguishes the fact that *in vitro* studies define a hazard, but are not alone considered reliable for predicting safety margins. Line 268 should be modified to indicate “hazard”.
15. Section 3.4.1.1, second paragraph. It is suggested that changes by the test substance on the QRS interval also be monitored to assess whether any observed QT changes are a result, in whole or in part, to changes in conduction.